REMARKS

Status of the Claims

By virtue of the Listing of Claims presented herein, claims 124, 132-137, 139-143, 145-150, 155-159, and 163-174 are pending. Claim 175 has been canceled. Claims 124, 132-135, 139-143, 145-150, 155-159, and 163-174 have been amended to enhance clarity, as well as correct minor grammatical and typographical errors. Basis for the amendments to claims 124, 132-135, 139-143, 145-150, 155-159, and 163-173 may be found in the instant application, for example: at page 51, line 1, through page 52, line 8, which discloses that expression control sequences include promoter sequences, describes the term "promoter sequence" as, for example, a DNA regulatory region, and describes that such expression control sequences, which include promoters, may be operatively linked to DNA sequences such that the DNA sequences may be expressed; at page 83, lines 21-24, which disclose that adenoviruses and adeno-associated viruses may be employed to harbor a gene encoding the claimed OB polypeptides and for use in the claimed methods; and throughout the specification, including the Examples, which discloses that a consequence of OB administration to a subject may be, for example, a decrease in body weight. Basis for the amendments to claims 150 and 174 may be found, for example, at page 84, line 25, through page 85, line 6, which discloses that attenuated and/or defective adenoviruses and adeno-associated viruses may be employed in the claimed methods. Thus, no new matter has been introduced by the amendments to the claims.

Claim Objections

The Examiner asserts that the claims should be amended to recite methods for decreasing body weight. Without acquiescing to the Examiner's assertion, and in order to advance prosecution of the instant case, Applicant has provided the suggested amendments as described above.

The Examiner repeats his objection under 35 U.S.C. § 132(a) to the amendment of recitations of "84%" identity to "83%" identity on pages 12 and 102 of the specification, as allegedly introducing new matter. The Examiner asserts that because there are allegedly "numerous methods for calculating percent identity", and "it is not readily apparent that applicants' new calculation used the same method as the one originally used or that 84% as

originally disclosed was simply a calculation error", the indicated amendments constitute new matter. Applicants disagree, for the reasons set forth in previous responses as well as the reasons provided below. The portion of the specification in question, as originally filed, describes the overall percent identity at the amino acid level between mouse and human OB sequences disclosed in Figure 4. The meaning of the term "identity" is clear and unambiguous, and in the context of an amino acid sequence alignment of two sequences of equal length, wherein no gaps are present, refers to the extent to which the two sequences are identical or not identical at the amino acid level. Specifically, as is the case in Figure 4, a reference to overall percent identity clearly refers to that proportion of the total number of amino acids in each sequence (here 167 amino acids) which are identical between the two sequences, expressed as a percentage. This simple and unambiguous relationship is expressed as the following art-recognized formula:

Overall % identity =

((total # of amino acids – # of non-identical amino acids)/(total # of amino acids))(100).

Inspection of the one-letter amino acid code of the sequences of Figure 4 clearly and unambiguously informs the skilled artisan: 1) the total number of amino acids of each sequence (here, 167); and 2) the number of amino acids that are non-identical relative to the two sequences (here, 28). Applying these values to the simple expression above yields the value of 83%. Therefore, the overall percent identity between the sequences in Figure 4 is clearly, unambiguously, and inherently 83%. As such, the amendment to the specification as provided in previous responses does not constitute new matter, and finds inherent and unambiguous basis in the alignment of the two sequences provided in Figure 4 as originally filed. Accordingly, the new matter objection is in error and should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: Enablement

Claims 124, 132-137, 139-143, 145-149, 155-159, and 163-173 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner's repeated allegation of lack of enablement is predicated on the notion that "at the time of filing and since, the combination of vector, promoter, dosage, target tissue, level of expression, and route of administration required to target the desired tissue so that a therapeutic [effect] would occur was unpredictable". The Examiner points to Feldman et (1995) Miller et al. (1995), Crystal et al. (1995), Verma et al. (1997), Deonarian et al. (1998), and Ross et al (1996), in an effort to support his allegation.

Notwithstanding the fact that many of these references post-date the priority date of the instant application, the Examiner's characterization of the references denotes the broad, generalized nature of their alleged teachings. Accordingly, the Examiner applies these references in an equally broad and generalized manner, and has failed to articulate how such broad alleged teachings bear on the subject matter as claimed by Applicant. Indeed, none of the references are germane to the subject matter as claimed by the applicant: namely, methods of decreasing body weight, or for treating obesity, in a mammal by administration to the mammal an adenoviral vector or an adeno-associated vector comprising a nucleic acid sequence encoding an OB polypeptide according to the recitations of the claims in a therapeutically effective amount such that the mammal exhibits a decrease in body weight; methods of delivering DNA encoding such OB polypeptides; or methods of expressing such OB polypeptides from such vectors. The courts have held that such generalizations are not sufficient to support a finding of nonenablement. Further, the issue of enablement, particularly undue experimentation, must be decided on the facts of the case (see, e.g., *Ex Parte Goeddel*, 5 U.S.P.Q.2d 1449, 1450 (Bd. Pt. App. & Int. 1985), and *Parte Kung,* 17 U.S.P.Q.2d 1545, 1546 (Bd. Pt. App. & Int. 1989).

Tellingly, the Examiner's own characterization of the references of record that are relevant to claimed methods, i.e., reducing weight by administration of OB-polypeptide-encoding adenovirus or adeno-associated virus supports, rather than negates, the enabling aspect of the instant application with respect to the methods claimed herein. Indeed, as illustrated by the Examiner's synopsis of each of the Fletcher et al. (1995), Morsy et al. (1998), and Muzzin et al. (1996) references, these references collectively demonstrate that, in fact, selection of a singular, or even particular, OB protein-encoding adenovirus dosage or titer, route of administration, modality by which vector is delivered (e.g., injection of vector suspension or implantation of vector-transfected cells), or target tissue (transplanted bone marrow cells, in vivo transfected

adipocytes, etc.) is not critical in order to practice the claimed methods and achieve a therapeutic effect as instantly claimed.

However, despite the non-essential nature of such parameters in practicing the claimed methods, as demonstrated by, for example, Fletcher et al. (1995), Morsy et al. (1998), and Muzzin et al. (1996), the Applicant's disclosure nonetheless provides ample guidance as to the selection of suitable combinations of such parameters which may be considered in order to practice the methods as instantly claimed, and provides reagents, and criteria, etc. by which such selections may be made. For instance, the instant Application provides numerous vectors and vector elements, including the recited adenovirus and adeno-associated virus vectors, promoter and other elements, as well as transfection reagents and methodologies (see, e.g., page 54, line 1-19; page 83, line 21, through page 85, line 10); determination and assessment of a therapeutically effective amount, e.g., by ascertaining observable endpoints, such as weight loss (see, e.g., page 72, line 5, to page 73, line 6). The references demonstrate that the claimed methods are fully enabled by the Applicant's disclosure, and that whereas ample guidance is provided in the instant application for the selection of conditions such as viral dosages/titers, routes of administration, target tissue, etc., no one particular chosen set of such conditions, is critical in order to achieve the claimed therapeutic effect. Thus, the selection of such parameters, in light of the skill and knowledge of the skilled artisan and the guidance provided in the instant application, is not only fully enabled, but also routine.

Nonetheless, in order to shore up the enablement rejection of the claimed methods, the Examiner claims that "the specification and art since the time of filing are limited to treating mammals with an ob deficiency", and that "the specification does not provide an enabled use for decreasing the body weight of a wild-type mammal (having normal weight)". This is incorrect. The instant application clearly demonstrates that a decrease in body weight is achieved in wild-type animals injected with an ob gene product, and also that human OB is active in mice (see, e.g., page 5, line 10-14; page 125, line 26 through page 126, line 2; and page 126, Table I).

Next, the Examiner alleges that because "certain claims encompass using <u>any</u> (emphasis added) analog of an ob protein that modulates body weight," and because "the specification defines analogs as ob proteins that agonize <u>or</u> antagonize the function of the ob protein," it would require one of ordinary skill in the art undue experimentation to determine antagonistic analogs

of the ob protein or how to use vectors encoding ob proteins capable of increasing (emphasis added) body weight." This allegation is incorrect insofar as, at least, the claims as amended herein are directed to methods of decreasing body weight in mammals administered the recited OB-encoding vectors. Additionally, each of the claims do not read on "any" analog, but are directed to a genus of analogs that are generated, for example, by substitution at one or more specific positions that are disclosed as amenable to such substitution without a substantial decrease in weight loss activity. Similarly, the Examiner asserts that "the specification does not define what [it] considers 'conservative' and 'non-conservative' substitutions." Again, the instant claims are directed to, for example, substitution at one or more recited positions, and do not include any recitation to "conservative" or "non-conservative" substitutions. Thus, the Examiner's rejection on the grounds that these terms are not defined is moot. Even assuming *arguendo* that such definitions are relevant to enabling the instant claims, Applicant's submit that the meaning of such terms in the context of the relevant art were well established and recognized at the time of the priority date of the instant application, such that the skilled artisan would construe their meaning in the context of the substitutions recited in the instant claims as clear and fully enabled.

The Examiner next urges that Applicants "have not adequately taught how to target OB expression to its native expressing tissue or to target OB to the tissue in which it mediates its effects." Further, the Examiner claims that "determining the tissue to target is only the first of a number of hurdles applicants have left for those of skill to perform the method claimed." As mentioned above, the Examiner's own synopsis of the cited references demonstrate that neither target tissue, nor OB "native expressing tissue" is required to be targeted by the claimed OB-encoding vectors in order to practice the claimed methods in order to achieve the claimed therapeutic effect. Further, the instant Applicant teaches the non-necessity of targeting such OB target tissues or "native expressing tissues". The instant application teaches that the ob gene product is "a circulating factor, such as a hormone" that is "secreted by cells that express it" (see e.g., page 25, line 24, through page 26, line 7); as such, ectopic expression by OB-encoding adenoviral-transfected cells of such a OB circulating factor reasonably achieves the same result as ob gene product secreted by a "native expressing tissue." The nature of the tissue is not relevant, and therefore, targeting of a particular tissue is not an essential feature of the claimed

methods. Indeed, the Examples in the instant application, which demonstrate that administration of OB protein by injection (i.e., into the circulation of the test animal), without consideration of OB tissue origin or OB target tissue achieves a therapeutic effect of a decrease in body weight (see, e.g., page 5, line 10-14; page 125, line 26 through page 126, line 2; and page 126, Table I). Thus, not only is targeting of a particular OB-sensitive or OB "native expressing" tissue not a claimed element, it is not an essential feature in practicing the methods as claimed in order to achieve the recited therapeutic effect.

For the foregoing reasons, as well as those provided in previous responses, the rejection of the claims as amended herein under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement is without merit and should be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph: written description

The Examiner has rejected claims 124, 132-137, 139-143, 145-149, 155-159, and 163-173 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner asserts that the phrases "operatively linked to a promoter" and the recitation of "83% or more amino acid identity to the OB polypeptide amino acid sequence set out in SEQ ID NOs:2, 4, 5, 6, 23, or 25" constitute new matter. For the reasons provided in the Status of the Claims and Objections sections, these new matter rejections are traversed. Ample written description is provided for the phrases as they appear in the claims as amended herein.

The Examiner next asserts that "the concept of an OB protein comprising 'amino acids 22-167 of SEQ ID NO:4 wherein one or more amino acids selected from the group consisting of amino acids 53...166 is substituted with another amino acid' " in claims 134, 142, 148, and 158 is new matter. For the reasons presented in previous responses, as well as the reasons below, this rejection is traversed.

Analysis

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618

(Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also, Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987).

As outlined in the Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112 paragraph 1, "Written Description" Requirement (Docket No. 991027288-0264-02; OG date January 30, 2001), the inquiry for compliance with the written description requirement where claims are directed to a genus is performed by: 1) assessing the degree of variation among species within the genus, and 2) making a determination as to whether a representative number of examples are either explicitly or implicitly described in the application, as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species.

To this end, as outlined in the Guidelines:

> the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

Further,

> a satisfactory 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

The instant specification, discloses, for example, that: (1) interspecies OB polypeptides homology is high, and as much as greater than 80% homologous (see, e.g., page 5, line 25, through page 6,line 2); (2) the primary sequences of mouse and human OB polypeptides identified in vivo and disclosed in full by Applicant (SEQ ID NOS: 2 and 4 respectively) share 83% amino acid sequence homology (notwithstanding an inadvertent typographical error in which "83%" was typed as "84%" as explained in previous responses as well as the comments

above; also see e.g., Figure 4 and page 12, lines 15-23, as amended herein); (3) both mouse and human OB polypeptides (SEQ ID NOS: 2 and 4, respectively) are capable of modulating body weight when administered to ob/ob mice and wild-type mice (e.g., page 5, lines 6-14 and in the Examples, throughout); (4) OB-encoding polynucleotides of essentially the same size as the disclosed mouse OB polynucleotide sequence were isolated and identified based on high homology to an entire exon (SEQ ID NO:7) of the mouse OB-encoding sequence (see, e.g. Figure 16 and page 95, lines 9-21); (5) mouse and human OB polypeptide polymorphic forms exist in vivo, characterized by deletion of glutamine at position 49 (see, e.g., Figures 5 and 6, page 12, line 24 through page 13, line 8, and SEQ ID NOS: 5 and 6); (6) numerous exemplified amino acid positions that are not essential for activity may be substituted by numerous exemplified amino acids, based on the sequence alignments between mouse and human OB proteins, as well as on disclosed structural information (see, e.g., page 32, line 6, through page 35, line 23); and (7) each identified mouse and human polypeptide demonstrated to be cleaved to remove an N-terminal 21-amino acid signal sequence (see, e.g. pages 12 and 13, and Figures 3, 4, 5 and 6), assays for weight modulatory and food intake inhibition activity of OB polypeptides, and exemplary results obtained therefrom (see, e.g., Example 8 (pages 112-130), and Figures 28A-28D). Therefore, Applicant has described multiple OB polypeptides possessing weight modulatory capability as a common functional feature, and possessing from zero (0) percent to 17% amino acid sequence variability, respectively (i.e., possess 100% and as little as 83% amino acid sequence identity relative to one another) as a common structural feature.

Accordingly, the inquiry with respect to item 1) above reveals that there is little substantial degree of variation between species within the claimed genus: the OB polypeptide amino acid sequences as recited in the claimed methods are capable of modulating body weight, and are described in the instant specification (SEQ ID NOS:2, 4, 5, or 6). Thus, contrary to the Examiner's assertion that "the specification is limited to specific amino acid difference (sic) at the positions claimed (except 56 and 95), and does not suggest substituting amino acids at the positions claimed with any amino acid as broadly claimed," is new matter, the degree of variation within the claimed genus is fully exemplified and described in the instant application as filed.

The assessment with respect to item 2) of the inquiry similarly reveals that the instant application describes a representative number of examples, either explicitly or implicitly, such

that the skilled artisan would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species. In this regard, and as explained in previous responses as well as in the analysis above, the instant application provides an amino acid sequence alignment of mouse and human OB polypeptides, and indicates 28 positions at which differences between the sequences are observed, which translates to 83% sequence identity between the two sequences (see, e.g. Figure 4). Figure 4 thus inherently discloses, as the skilled artisan would recognize, OB polypeptides that differ from either the mouse or human sequence depicted in Figure 4 by one, two, three, four, five, six, seven, eight, nine, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 amino acids, corresponding to OB polypeptide sequences possessing 99.4%, 98.8%, 98.2%, 97.6%, 97.0%, 96.4%, 95.8%, 95.2%, 94.6%, 94.0%, 93.4%, 92.8%, 92.2%, 91.6%, 91.0%, 90.4%, 89.8%, 89.2%, 88.6%, 88.0%, 87.4%, 86.8%, 86.2%, 85.6%, 85.0%, 84.4%, 83.8%, or 83.0%, respectively. Thus, there can be no doubt that a representative number of species encompassed by the claimed genus are described, either explicitly or inherently, such that the skilled artisan would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species. Accordingly, the rejection is erroneous and should be withdrawn.

The Examiner reiterates the contention that the recitation that amino acid positions 56 and 95 may be substituted as recited in claims 134, 142, 148, and 158 constitutes new matter because these positions are alleged to not be different between mouse and human OB as aligned in Figure 4. The Examiner also states that "Applicants do not argue this rejection." The Examiner is incorrect on both counts. Figure 4, in fact, does illustrate that the amino acids at positions 56 and 95 differ between mouse and human OB sequences: in mouse, positions 56 and 95 are shown to be arginine (R) and leucine (L), respectively; in human, positions 56 and 95 are shown to be lysine (K) and isoleucine (I), respectively. Substitution at these positions is therefore described and contemplated by the instant application. Applicant notes that at page 26, lines 9-22, of Applicant's response filed June 29, 2006, this rejection of the recitation was addressed and rebutted. Therefore, for the reasons provided herein as well as the reasons provided in previous responses, the rejection is erroneous and should be withdrawn.

The Examiner's next rejection, which is directed to "the concept of an OB protein comprising 'amino acids 22-166 of SEQ ID NO:6 wherein one or more amino acids selected from the group consisting of amino acids 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 is substituted with another amino acid' ", as recited in claims 135, 143, 149, and 159, alleges that this recitation constitutes new matter insofar as the specification allegedly "does not suggest substituting the amino acids in the Gln deleted mutants in Fig. 5 and 6, specifically with any amino acid as broadly claimed."

Applicants traverse: the analysis described above yields the same result with respect to the claimed genus Gln deleted OB proteins. Therefore, the rejection is without merit and should be withdrawn.

The Examiner next reiterates the rejection of claims 166-173, allegedly that they constitute new matter insofar as the support argued by Applicants in previous responses is not found in the specification. Applicants traverse: support for rejected substitutions is found in the portions of the specification to which the Examiner was directed in previous responses (i.e., pages 32 through 35 – see page 27, lines 20-24 of response filed June 29, 2006). Additionally, with respect to: subparts (a); (b); (c); (d); (e); (f); and (g) of claim 166, the Examiner is invited to inspect, respectively: page 134, line 27, through page 35, line 2; page 35, line 2; page 35, lines 3-4; page 35, line4; page 35, line 5; page 33, lines 7-8; and page 34, lines 5-11. With respect to: subparts (a); (b); and (c) of claim 170, the Examiner is invited to inspect, respectively: page 32, line 21-page 33, line 2, in conjunction with page 33, lines 11-14, which describes analogs as recited in the each of subparts (a); (b); and (c) of claim 170. With respect to: subparts (a); (b); (c); (d); (e); (f); and (g) of claim 171, the Examiner is invited to inspect the disclosure found in the specification as outlined above for claim 166 in conjunction with that outlined above for 170. With respect to: subparts (a); (b); (c); (d); (e); (f); (g); and (h) of claim 173, the Examiner is invited to inspect the disclosure at page 54, line 24, through page 55, line 19, Figures 22A-22C and 22A-22B, and the amino acid sequences provided in the recited SEQ ID NOS, which collectively discloses the amino acid sequence of the recited tags/sequences (e.g., HIS-tags, remnants of KEX-2 or thrombin cleavage of exogenous, vector-derived (e.g., "non-OB") sequences), and discloses that they may be fused to the N-terminus of an OB protein as recited in the claims. With respect to the subparts, (a) through (h)(8), of each of claims 169 and 172, the

Examiner is invited to inspect the portions of the specification outlined in the portions of the specification outlined for each of claims 166, 167, 168, 170, 171, and 173. Accordingly, the Rejection of claims 166, 167, 168, 169, 170, 171, 172, and 173 is in error and should be withdrawn.

The Examiner next rejects claims 124, 132-137, 139-143, 145-149, 155-159, and 163-173 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement because the specification allegedly "does not provide written description for the 'therapeutically effective amount' of a vector administered to a mammal 'such that the mammal exhibits a decrease in body weight'. Applicants traverse.

Contrary to the Examiner's assertion, the instant specification provides ample description of determination of a therapeutically effective amount, of example at page 72, lines 5-9 and page 72, line 25, through 73, line 5, which discloses that a therapeutically effective amount comprises an amount sufficient to reduce a clinically significant deficit in the recited activity function, or response of the host by at least about 15 percent, at least 50 percent, by at least 90 percent, or to prevent such a deficit. A therapeutically effective amount is disclosed to alternatively comprise an amount sufficient to cause an improvement in a clinically significant condition in the host by, for example, these benchmark values. The instant application also discloses that treatment of, for example, abnormal elevation of body weight is a clinically significant condition for which a therapeutically effective amount of the recited OB-encoding vectors may be administered in the claimed methods in order to achieve a decrease in body weight (see, e.g., page 11, lines 5-8). Therefore the recitation of a "therapeutically effective amount" enjoys satisfactory written description support in the application as filed. Accordingly, the rejection of the claims is in error and should be withdrawn.

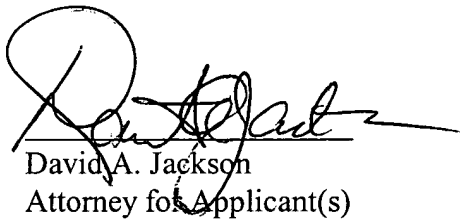
The remainder of the Office Action simply repeats the rejections already outlined, responded to, and traversed as described above, and is therefore considered by Applicant to have been fully responded to. Accordingly, Applicants believe that all issues raised in the Office Action have been properly addressed in this response and in the amendments to the claims as shown in the attached Listing of Claims. Accordingly, reconsideration and allowance of the amended claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact

Applicants' representative at the telephone number below.

CONCLUSION

No fees in addition to the extension fees mentioned above are believed due for this submission. However, if a fee is due, the Commissioner is hereby authorized to charge payment of any fees associated with this communication, to Applicant's Deposit Account No. 11-1153 referencing Docket No. 600-1-087-CIP2I. Additionally, the Commissioner is hereby authorized to charge payment or credit overpayment of any fees during the pendency of this application to Applicant's Deposit Account No. 11-1153.

Respectfully submitted,



David A. Jackson
Attorney for Applicant(s)
Registration No. 26,742

KLAUBER & JACKSON, LLC.
411 Hackensack Avenue
Hackensack NJ 07601
Tel: (201) 487-5800

Date: March 14, 2007